HSIA STATEMENT ON PROPOSED LISTING OF TRICHLOROETHYLENE AS SUBSTANCE "REASONABLY ANTICIPATED TO BE A HUMAN CARCINOGEN" IN THE NINTH REPORT ON CARCINOGENS

The criteria that guide the decision to list a substance in the Report on Carcinogens were described by the National Toxicology Program (NTP) in its September 1996 Criteria for Listing Agents Substances or Mixtures in the Biennial Report on Carcinogens. This document contains the following statement:

> Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information. Relevant information includes, but is not limited to, dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive subpopulations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance. For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals but there are compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans.

The Halogenated Solvents Industry Alliance, Inc. (HSIA) urges that the review of trichloroethylene for possible listing in the Report on Carcinogens be postponed until the conclusion of a broader reassessment of the potential carcinogenicity of trichloro-

ethylene currently underway under the leadership of the Environmental Protection Agency (EPA) is completed. The factors that EPA must consider in reassessing the evidence as to the potential carcinogenicity of trichloroethylene under its guidelines are essentially the same factors that are to be taken into account in the NTP listing decision. Thus, the EPA reassessment, which is being conducted under EPA's proposed revised guidelines for carcinogen risk assessment, 61 Fed. Reg. 17959 (Apr. 23, 1996), will cover in detail the same information identified as relevant in the September 1996 NTP Criteria document, and addressed in the draft RC Background Document for Trichloroethylene (Sept. 30, 1997).

The EPA reassessment was initiated in June 1996, and encompasses a comprehensive review of available scientific information on trichloroethylene, including a great deal of relevant mechanistic research sponsored by EPA, the Department of Defense, and the Department of Energy. A description of this reassessment from EPA, including a timetable, is attached. We encourage NTP to coordinate with EPA to determine the status of the reassessment and obtain an evaluation of the views of those involved in the reassessment as to the significance of the available mechanistic and metabolic information for the hazard identification process. NTP may find, for example, that some of the rationale as to the biological plausibility of the observed kidney tumors reflected in the draft RC Background Document for Trichloroethylene, such as the presumed dichlorovinylcysteine pathway, is being called into serious question.

As may be seen from the description of the EPA reassessment, a significant amount of attention is devoted to determination of the mode(s) of action for site- specific carcinogenic effects observed in rodents. Subjects under review include:

- the metabolic fate and disposition of trichloroethylene, including a discussion of metabolic pathways and inferences for cross-species and high-to-low dose differences;

- hypotheses as to the roles of trichloroacetic acid, dichloroacetic acid, chlorohydrate, and metabolites produced via the glutathione pathway in the induction of liver carcinogenicity, with an emphasis on high-to-low dose and species differences in the identified modes of action and including a discussion of the possible roles of genetic toxicity, peroxisome proliferation, and oncogene activation in liver toxicity;

- hypotheses as to the role of trichloroethylene metabolites in the production of kidney carcinogenicity, including the genetic toxicity of metabolites and implications for kidney carcinogenicity, as well as species differences and similarities in metabolism and sensititity;

- pharmacokinetic models for dosimetric adustment, other approaches for dose response analyses, and uncertainty in pharmacokinetic models.

The Draft RC Background Document for Trichloroethylene relies heavily on the conclusions from the February 1995 IARC Monograph[1] rather than an updated independent evaluation. The draft appears to summarize the written conclusions from individual articles without a thorough integrated evaluation that considers mechanistic data, interspecies variability, and applicability to risk assessment. Furthermore, EPA's proposed revised guidelines for carcinogen risk assessment define seven well-accepted criteria to determine the value of epidemiology studies and their usefulness in assessing cancer risk. The NTP should ensure that its epidemiologists adopt these criteria to fully evaluate the strength and limitations of the available epidemiology studies for trichloroethylene and their usefulness in assessing human risk.

As indicated above, the reassessment being coordinated by EPA will examine in detail the scientific evidence that is the basis for a judgment by NTP as to whether trichloroethylene should be listed as "reasonably anticipated to be a human carcinogen." To avoid duplicative and possibly inconsistent reviews, we urge NTP to await the completion of the reassessment of trichloroethylene under the EPA guidelines before considering whether it should be listed in the Report on Carcinogens. Executive Order

[1] Vol. 63, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Dry Cleaning, Some Chlorinated Solvents and Other Industrial Chemicals (1995).

12866 requires agencies to avoid taking regulatory action that is duplicative or inconsistent with action taken by other agencies.[2]

Finally, significant new studies relating to the mechanism of action and epidemiology of trichloroethylene have been published and must be evaluated as part of any hazard identification process. They include Species Differences in Carcinogenicity: The Role of Metabolism in Human Risk Evaluation, Teratogenesis, Carcinogenesis, and Mutagenesis 10:103-113 (1990); Melanoma and Occupation: Results of a Case-Control Study, Occup. Environ. Med. 53:168-173 (1996); A Critical Review of Epidemiology Studies of Trichloroethylene and Perchloroethylene and Risk of Renal-Cell Cancer, Int. Arch. Occup. Environ. Health 70:222-231 (1997); The Role of Glutathione Conjugation in the Development of Kidney Tumours in Rats Exposed to Trichloroethylene, Chem. Biol. Interact. 105:99-117(1997).

Attachments

[2] In this regard, both listing in the Report on Carcinogens and EPA's carcinogen classification decisions have been determined by the federal courts to be regulatory in effect. *SOCMA v. DHHS*, 720 F. Supp. 1244 (W.D. La. 1989): *Flue-Cured Tobacco Coop. Stabilization Corp. v. EPA* 857 F. Supp. 1137 (M.D.N.C. 1994).

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

February 4, 1997

OFFICE OF
RESEARCH AND DEVELOPMENT

Peter Voytek, Ph.D.
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Suite 5064
Washington, D.C. 20036

Dear Dr. Voytek:

Thank you for making time in your busy schedule to serve on the External Involvement Group for our trichloroethylene assessment. We'd like to let you know the status of the assessment and give you an opportunity to comment.

As you will recall from our letter of June 12, the assessment is being written in two parts, a set of state-of-the-science papers, followed by a synthesis and risk characterization. Since last summer, the authors have been writing their state-of-the-science papers, and we have received drafts from most of them. Enclosed for your information is a list of state-of-the-science papers comprising the first part of the assessment.

We will soon begin writing the second part of the assessment, the synthesis and risk characterization. Enclosed for your comment is an outline of the synthesis and risk characterization. It will focus on a series of hazard, dose-response, and exposure characterization issues. Please take a few minutes to look over the outline. If you would like to suggest additional issues for us to consider, please let us know by February 28.

We expect to complete a draft in the summer. Then the assessment will be reviewed and revised, starting with a review by EPA scientists and progressing to a review by an external panel of independent experts in a public meeting, hopefully, before the end of the year. We received some suggestions for peer reviewers in response to the June 12 letter. In a few months we will give you another opportunity to suggest peer reviewers. Later this year we will send you a copy of the assessment, just as soon as it is cleared for release.

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Enclosed you will find a fact sheet that provides more information about the trichloroethylene assessment. Please feel free to distribute the fact sheet and the outlines to your colleagues.

Thank you once again for your contributions to this endeavor. Your participation as a representative of the broader scientific community will improve both the scientific credibility and the public acceptance of the assessment. If you have any questions or comments, please call either Jim Cogliano or Cheryl Siegel Scott at 202 2603814.

Sincerely yours,

Michael Callahan
Director, Washington Office
National Center for Environmental Assessment

Enclosures

Distribution:
Melvin E. Andersen, Ph.D., ICF/Crump Kaiser
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Peter Voytek, Ph.D., Halogenated Solvents Industry Alliance
Lauren Zeise, Ph.D., California Environmental Protection Agency

HAZARD ASSESSMENT

Metabolism of trichloroethylene. Lawrence Lash and Jean Parker.

Overview of the genetic toxicity of trichloroethylene and its metabolites. Martha Moore.

Modes of action for kidney tumorigenesis. Lawrence Lash and Jean Parker.

Mode of action for liver toxicity by trichloroethylene. Richard Bull and Tony DeAngelo.

Mode of action for lung toxicity. Trevor Green.

Evaluation of the epidemiologic evidence for making inferences of cancer hazards and risks for exposure to trichloroethylene. [Author to be selected through competitive procurement].

Sensitive populations. Wendy Yap and Maria Carroquino.

DOSE-RESPONSE ASSESSMENT

Development of a physiologically based pharmacokinetic model of trichloroethylene and its metabolites for use in risk assessment. Harvey Clewell.

Physiologically based pharmacokinetic models for trichloroethylene and its oxidative metabolites in mice and humans. Jeffrey Fisher.

Dose metrics for acute neurological effects ($C \times T$ versus C). Will Boyes, Phil Bushnell, and Kevin Crofton.

Noncancer effects due to trichloroethylene: pharmacokinetics and risk assessment. Hugh Barton.

Dose-response approaches for modeling trichloroethylene carcinogenicity data. Lorenz Rhomberg.

Uncertainty associated with a pharmacokinetic model applied to a dose-response assessment of trichloroethylene carcinogenicity data. Frederic Bois.

Uncertainty associated with the Fisher et al. pharmacokinetic models applied to dose-response assessment of trichloroethylene carcinogenicity data. Frederic Bois.

Biologically based dose-response modeling. Chao Chen.

EXPOSURE ASSESSMENT

Sources, emissions, and exposure for trichloroethylene and its metabolites. Jonathan Becker.

PART II. SYNTHESIS AND RISK CHARACTERIZATION: EPA's POSITION

27 Jan 97

INTRODUCTION

[Historical background, structure of this piece.]

ISSUES IN HAZARD CHARACTERIZATION

Issue 1. What happens to trichloroethylene in the body? *[Set up the issues that follow by qualitatively identifying metabolites and target organs.]*

Issue 2. What do the epidemiologic studies indicate about an association between trichloroethylene exposure and cancer?

Issue 3. What do the epidemiologic studies indicate about an association between trichloroethylene exposure and other adverse effects?

Issue 4. What do the cancer studies in laboratory animals indicate about trichloroethylene and its metabolites?

Issue 5. What do genetic toxicity tests indicate about trichloroethylene and its metabolites?

Issue 6. What do the mechanistic studies indicate about the relevance of these results to humans?

Issue 7. What research could potentially resolve the open questions about the cancer hazard to humans?

Issue 8. What do the studies in laboratory animals indicate about noncancer effects?

Issue 9. Which noncancer effects have not been adequately studied?

Issue 10. Considering information on potential modes of action, can highly sensitive populations be identified? *[Include statement about children.]*

ISSUES IN DOSE-RESPONSE CHARACTERIZATION

Issue 11. Considering the pharmacokinetic modeling, which dose metrics are viable, and how should they be scaled from animals to humans?

Issue 12. What do the pharmacokinetic studies indicate about uncertainty or variability in the dose metrics across the human population?

Issue 13. Considering information on potential modes of action and the availability of experimental results to estimate model parameters, what are the viable approaches to cancer dose-response modeling in the observed range?

Issue 14. What is the evidence to support either linear or nonlinear extrapolation to lower levels?

Issue 15. How does cumulative exposure to other sources of trichloroethylene metabolites affect the risk from incremental exposure to trichloroethylene?

Issue 16. Which approach does EPA select at this time for quantifying cancer risks from trichloroethylene?

Issue 17. What research could potentially resolve the open questions about the cancer dose-response assessment?

Issue 18. Considering information on dose, severity of effects, and shape of the dose-response curves, which noncancer effects are the critical effects for determining an RfD or RfC?

Issue 19. What RfD and RfC will EPA use at this time?

Issue 20. What research could potentially resolve the open questions about the noncancer dose-response assessment?

ISSUES IN EXPOSURE CHARACTERIZATION

Issue 21. What are the principal sources of human exposure to trichloroethylene?

Issue 22. What are the principal sources of human exposure to the metabolites of trichloroethylene?

Issue 23. What are the principal pathways of human exposure to trichloroethylene and its metabolites?

Issue 24. What can be said about different segments of the population and their levels of exposure to trichloroethylene and its metabolites?

Issue 25. Which populations are highly exposed? *[Include statement about children.]*

Issue 26. What research could potentially resolve the open questions about the exposure assessment?

SUMMARY OF GUIDANCE FOR RISK ASSESSORS

EXAMPLES

FACT SHEET TRICHLOROETHYLENE HEALTH RISK ASSESSMENT 27 Jan 97

Background

Trichloroethylene (TCE) is a major contaminant of concern in EPA's air, water, and waste programs. It is found at one-third of Superfund sites. EPA's 1985 assessment and 1987 draft addendum concluded that TCE is potentially carcinogenic to humans, although in 1989 the assessment was withdrawn from IRIS (EPA's Integrated Risk Information System) pending resolution of the classification as either "possibly" or "probably" carcinogenic to humans. Since that time, new studies have provided information on how TCE causes cancer. EPA's National Center for Environmental Assessment (NCEA) is evaluating this information to update its characterization of TCE's health risks.

What will the new TCE assessment cover?

The assessment is being written in two parts. First is a set of state-of-the-science papers written by experts mostly from outside EPA, many of whom are actively conducting research on TCE. They will present a balanced discussion of key research results, plausible scientific interpretations of these results, and strengths and limitations of the scientific information supporting each plausible interpretation.

Second will be a synthesis and risk characterization, where EPA will draw from the state-of-the-science papers to update its position on TCE's health risks. Using its 1996 proposed cancer guidelines, EPA will update its position on the likelihood that TCE causes cancer. A qualitative assessment will focus on the mechanisms by which TCE causes cancer and their relevance to humans. A quantitative assessment will describe dose-response relationships, taking into account scaling from animals to humans and from high to low doses. In addition, EPA will assess the noncancer toxicity of TCE for the first time, deriving an oral reference dose (RfD) and an inhalation reference concentration (RfC).

The health risk assessment does not change EPA's standards under its air, water, or waste programs. After the assessment has been completed, EPA's regulatory programs may consider whether changes are warranted. It would be premature to speculate at this time about the likelihood, timing, or effect of any potential changes.

What provisions have been made for external peer involvement?

EPA is involving the broader scientific community in the assessment. To assist in reaching out to scientists from all sectors, an External Involvement Group, composed of representatives from private industry, public interest groups, and state and federal agencies, will assist with (1) proposing topics for state-of-the-science papers and securing expert scientists as authors, (2) reviewing these papers for balance and completeness, (3) proposing topics for the synthesis and risk characterization, (4) nominating peer reviewers, and (5) keeping scientists from their sector informed.

What provisions will be made for external peer review?

The assessment will be reviewed by a panel of independent experts at a public meeting. The meeting will be announced in the Federal Register about 4 weeks in advance. Before the review is complete, the assessment will not constitute EPA policy.

What is the schedule?

Work began on the state-of-the-science papers in early 1996, and they should be substantially complete by the middle of 1997. An external review draft, comprising the state-of-the-science papers and the synthesis and risk characterization, should be available in October, and the review meeting could take place by December. EPA will incorporate the review panel's comments into a final assessment, which, assuming a favorable review, would be issued in 1998. At that time, a summary of the assessment will be loaded onto IRIS.

How can I get a copy of the draft assessment?

When the external review draft is available, a notice will appear in the Federal Register. The draft will be available on the WorldWide Web, or copies can be purchased from the National Technical Information Service (NTIS).

Whom can I call for more information?

You can call either Jim Cogliano or Cheryl Siegel Scott at 202 260–3814. This fact sheet will be updated as the information it contains changes.